

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV302402455US, in an envelope addressed to: MS Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: December 12, 2003 Signature:   
(Mark Jane DiPalma)

Docket No.: CIBT-P03-068  
(PATENT)

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:  
Dudek et al.

Application No.: Not Yet Assigned

Confirmation No.:

Filed: December 12, 2003

Art Unit: Not Yet Assigned

For: REGULATORS OF THE HEDGEHOG  
PATHWAY, COMPOSITIONS AND USES  
RELATED THERETO

Examiner: Not Yet Assigned

### INFORMATION DISCLOSURE STATEMENT (IDS)

MS Patent Application  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement accompanies the new patent application submitted herewith.

A copy of each reference on PTO/SB/08 are not supplied because they were previously cited by or submitted to the Office in a prior application number 09/867311, filed May 29, 2001 and relied upon in this application for an earlier filing date under 35 U.S.C. 120.

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this

Information Disclosure statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. CIBT-P03-068. A duplicate copy of this paper is enclosed.

Dated: December 12, 2003

Respectfully submitted,

By 

David P. Halstead, Ph.D.

Registration No.: 44,735

ROPES & GRAY LLP

One International Place

Boston, Massachusetts 02110-2624

(617) 951-7000

(617) 951-7050 (Fax)

Attorneys/Agents For Applicant

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO				<i>Complete if Known</i>	
				Application Number	Not Yet Assigned
				Filing Date	December 9, 2003
				First Named Inventor	Henryk Dudek
				Art Unit	N/A
				Examiner Name	Not Yet Assigned
Sheet	1	of	5	Attorney Docket Number	CIBT-P03-068

<b>U.S. PATENT DOCUMENTS</b>					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
AA	US-4,007,268	02-08-1977	Voorhees		
AB	US-4,353,888	10-12-1982	Sefton		
AC	US-4,634,706	01-06-1987	Kaneko et al.		
AD	US-4,751,224	06-14-1988	Agarwal et al.		
AE	US-4,892,538	01-09-1990	Aebischer et al.		
AF	US-4,955,892	09-11-1990	Daniloff		
AG	US-5,041,138	08-20-1991	Vacanti et al.		
AH	US-5,092,871	03-03-1992	Aebischer et al.		
AI	US-5,288,514	02-22-1994	Ellman		
AJ	US-5,359,115	10-25-1994	Campbell et al.		
AK	US-5,362,899	11-08-1994	Campbell		
AL	US-5,565,462	10-15-1996	Eitan et al.		
AM	US-5,712,171	01-27-1998	Zambias et al.		
AN	US-5,736,412	04-07-1998	Zambias et al.		
AO	US-5,789,439	08-04-1998	Hosono et al.		
AP	US-6,291,516	09-18-2001	Dudek et al.		

<b>FOREIGN PATENT DOCUMENTS</b>					
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)			
BA	EU-EP0020029A1		10-12-1980		
BB	WO-89/11487		11-30-1989		
BC	WO-91/07087		05-30-1991		
BD	WO-91/10743		07-25-1997		
BE	WO-92/10092		06-25-1992		
BF	WO-93/01275		01-21-1993		
BG	WO-93/09668		05-27-1992		
BH	WO-93/20242		10-14-1993		
BI	WO-93/21929		11-11-1993		
BJ	WO-94/08051		04-14-1994		
BK	WO-94/09229		04-28-1994		
BL	WO-94/10292		05-11-1994		
BM	WO-94/16718		08-04-1994		
BN	WO-98/58650		12-30-1998		
BO	WO-99/52534		10-21-1999		

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>1</sup>Applicant's unique citation designation number (optional). <sup>2</sup>See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup>Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup>For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup>Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup>Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature	Date Considered
--------------------	-----------------

<p>Substitute for form 1449A/B/PTO</p> <p><b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b></p> <p><i>(Use as many sheets as necessary)</i></p>				<b>Complete if Known</b>	
				Application Number	Not Yet Assigned
				Filing Date	December 9, 2003
				First Named Inventor	Henryk Dudek
				Art Unit	N/A
Examiner Name	Not Yet Assigned				
Sheet	2	of	5	Attorney Docket Number	CIBT-P03-068

<b>NON PATENT LITERATURE DOCUMENTS</b>					
Examiner Initials	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.			
	CA	Alcedo et al., "The drosophila smoothened gene encodes a seven-pass membrane protein, a putative receptor for the hedgehog signal," <i>Cell</i> 86:221-232 (1996)			T <sup>2</sup>
	CB	Altaba, "Restrictions to floor plate induction by hedgehog and winged-helix genes in the neural tube of frog embryos," <i>Mol. Cell. Neurosci.</i> 6:106-121 (1995)			
	CC	Apelqvist et al., "Sonic hedgehog directs specialized mesoderm differentiation in the intestine and pancreas," <i>Curr. Biol.</i> 7:801-804 (1997)			
	CD	Bellusci et al., "Involvement of Sonic hedgehog in mouse embryonic lung growth and morphogenesis," <i>Development</i> 124:53 (1997)			
	CE	Berge et al., "Pharmaceutical Salts," <i>J. Pharm. Sci.</i> 66:1-19 (1977)			
	CF	Bitgood et al., "Sertoli cell signaling by Desert hedgehog regulates the male germline," <i>Curr. Biol.</i> 6:298 (1996)			
	CG	Bitgood et al., "Hedgehog and Bmp Genes are coexpressed at many diverse sites of cell-cell interaction in the mouse embryo," <i>Dev. Biol.</i> 172:126-138 (1995)			
	CH	Bumcrot et al., "Proteolytic processing yields two secreted forms of sonic hedgehog," <i>Mol. Cell. Biol.</i> 15:2294-2303 (1995)			
	CI	Chang et al., "Products, genetic linkage and limb patterning activity of a murine hedgehog gene," <i>Development</i> 120:3339-3353 (1994)			
	CJ	Chen et al., "Analogous' organic synthesis of small-compound libraries: validation of combinatorial chemistry in small-molecule synthesis," <i>JACS</i> 116:2661 (1994)			
	CK	Chen et al., "Dual roles for patched in sequestering and transducing hedgehog," <i>Cell</i> 87:553-563 (1996)			
	CL	Davidson, "How embryos work: a comparative view of diverse modes of cell fate specification," <i>Development</i> 108:365-389 (1990)			
	CM	Dunnett et al., "Mechanisms of function of neural grafts in the adult mammalian brain," <i>J. Exp. Biol.</i> , 132:265-289 (1987)			
	CN	Echelard et al., "Sonic hedgehog, a member of a family of putative signaling molecules, is implicated in the regulation of CNS polarity," <i>Cell</i> 75:1417-1430 (1993)			
	CO	Ekker et al., "Distinct expression and shared activities of members of the hedgehog gene family of <i>xenopus laevis</i> ," <i>Development</i> 121:2337-2347 (1995)			
	CP	Ericson et al., "Sonic hedgehog induces the differentiation of ventral forebrain neurons: a common signal for ventral patterning within the neural tube," <i>Cell</i> 81:737-756 (1995)			
	CQ	Fan et al., "Patterning of mammalian somites by surface ectoderm and notochord: evidence for sclerotome induction by hedgehog homolog," <i>Cell</i> 79:1175-1189 (1994)			
	CR	Fan et al., "Long-range sclerotome induction by sonic hedgehog: direct role of the amino-terminal cleavage product and modulation by the cyclic AMP signaling pathway," <i>Cell</i> 81:457-465 (1995)			
	CS	Fietz et al., "Secretion of the amino-terminal fragment of the hedgehog protein is necessary and sufficient for hedgehog signalling in drosophila," <i>Curr. Biol.</i> 5:643-651 (1995)			
	CT	Forbes et al., "Hedgehog is required for the proliferation and specification of ovarian somatic cells prior to egg chamber formation in <i>Drosophila</i> ," <i>Development</i> 122:1125-1135 (1996)			
	CU	Francis et al., "Bone morphogenetic proteins and a signalling pathway that controls patterning in the developing chick limb," <i>Development</i> 120:209-218 (1994)			
	CV	Freed et al., "Neocartilage formation in vitro and in vivo using cells cultured on synthetic biodegradable polymers," <i>J. Biomed Mater Res.</i> 27:11-23 (1993)			
	CW	Freund et al., "Efferent synaptic connections of grafted dopaminergic neurons reinnervating			

Examiner Signature		Date Considered
--------------------	--	-----------------

Substitute for form 1449A/B/PTO				<b>Complete if Known</b>	
				Application Number	Not Yet Assigned
				Filing Date	December 9, 2003
				First Named Inventor	Henryk Dudek
				Art Unit	N/A
				Examiner Name	Not Yet Assigned
Sheet	3	of	5	Attorney Docket Number	CIBT-P03-068

		the host neostriatum: a tyrosine hydroxylase immunocytochemical study," <i>J. Neuroscience</i> 5:603-616 (1985)	
	CX	Fujita et al., "Involvement of sonic hedgehog in the cell growth of LK-2 cells, human lung squamous carcinoma cells," <i>Biochem Biophys Res Commun</i> 238:658-664 (1997)	
	CY	Gailani et al., "The role of the human homologue of <i>Drosophila</i> patched in sporadic basal cell carcinomas," <i>Nature Genetics</i> 14:78-81 (1996)	
	CZ	Goodrich et al., "Altered neural cell fates an medulloblastoma in mouse patched mutants," <i>Science</i> 277:1109-1113 (1997)	
	CA1	Goodrich et al., "Conservation of the hedgehog/patched signaling pathway from flies to mice: induction of a mouse patched gene by hedgehog," <i>Genes Dev.</i> 10:301-312 (1996)	
	CB1	Grande et al., "The repair of experimentally produced defects in rabbit articular cartilage by autologous chondrocyte transplantation," <i>J. Orthopaedic Res.</i> 7:208-218 (1989)	
	CC1	Gurdon, "The generation of diversity and pattern in animal development," <i>Cell</i> 68:185-199 (1992)	
	CD1	Hammerschmidt et al., "Protein kinase A is common negative regulator of hedgehog signalling in the vertebrate embryo," <i>Genes Dev.</i> 10:647-658 (1996)	
	CE1	Hidalgo et al., "Cell patterning in the <i>Drosophila</i> segment: spatial regulation of the segment polarity gene patched," <i>Development</i> 110:291-301 (1990)	
	CF1	Hooper et al., "The <i>drosophila</i> patched gene encodes a putative membrane protein required for segmental patterning," <i>Cell</i> 59:751-764 (1989)	
	CG1	Hui et al., "Expression of three mouse homologs of the <i>Drosophila</i> segment polarity gene <i>cubitus interruptus</i> , <i>Gli</i> , <i>Gli-2</i> , and <i>Gli-3</i> , in ectoderm- and mesoderm-derived tissues suggests multiple roles during postimplantation development," <i>Dev Biol.</i> 162:402-413 (1994)	
	CH1	Jensen et al., "Expression of sonic hedgehog and its putative role as a precursor cell mitogen in the developing mouse retina," <i>Development</i> 124:363 (1997)	
	CI1	Hynes et al., "Induction of midbrain dopaminergic neurons by sonic hedgehog," <i>Neuron</i> 15:35-44 (1995)	
	CJ1	Jessel, "Diffusible factors in vertebrate embryonic induction," <i>Cell</i> 68:257-270 (1992)	
	CK1	Johnson et al., "Exotopic expression of sonic hedgehog alters dorsal-ventral patterning of somites," <i>Cell</i> 79:1165-1173 (1994)	
	CL1	Johnson et al., "Human homolog of patched, a candidate gene for the basal cell nevus syndrome," <i>Science</i> 272:1668-1671 (1996)	
	CM1	Kinzler et al., "The GLI gene encodes a nuclear protein which binds specific sequences in the human genome," <i>Mol. Cell. Biol.</i> 10:634-642 (1990)	
	CN1	Krauss et al., "A functionally conserved homolog of the <i>drosophila</i> segment polarity gene <i>hh</i> is expressed in tissues with polarizing activity in zebrafish embryos," <i>Cell</i> 75:1431-1444 (1993)	
	CO1	Lai et al., "Patterning of the neural ectoderm of <i>xenopus laevis</i> by the amino-terminal product of hedgehog autoproteolytic cleavage," <i>Development</i> 121:2349-2360 (1995)	
	CP1	Laufer et al., "Sonic hedgehog and Fgf-4 act through a signaling cascade and feedback loop to integrate growth and patterning of the developing limb bud," <i>Cell</i> 79:993-1003 (1994)	
	CQ1	Lee et al., "Autoproteolysis in hedgehog protein biogenesis," <i>Science</i> 266:1528-1537 (1994)	
	CR1	Lee et al., "Secretion and localized transcription suggest a role in positional signaling for products of the segmentation gene hedgehog," <i>Cell</i> 71:33-50 (1992)	
	CS1	Lench et al., "Characterization of human patched germ line mutations in naevoid basal cell carcinoma syndrome," <i>Human Genetic.</i> , 100(5-6):497-502 (1997)	
	CT1	Leven et al., "molecular pathway determining left-right asymmetry in chick embryogenesis," <i>Cell</i> 82:803-814 (1995)	
	CU1	Lopez-Martinez et al., "Limb-patterning activity and restricted posterior localization of the amino-terminal product of sonic hedgehog cleavage," <i>Curr. Biol.</i> 5:791-795 (1995)	
	CV1	Mariño et al., "Biochemical evidence that patched is the hedgehog receptor," <i>Nature</i> 384:177-179 (1996)	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

<p>Substitute for form 1449A/B/PTO</p> <p><b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b></p> <p><i>(Use as many sheets as necessary)</i></p>				<b>Complete if Known</b>	
				Application Number	Not Yet Assigned
				Filing Date	December 9, 2003
				First Named Inventor	Henryk Dudek
				Art Unit	N/A
Examiner Name	Not Yet Assigned				
Sheet	4	of	5	Attorney Docket Number	CIBT-P03-068

	CW1	Marigo et al., "Conservation in hedgehog signaling: induction of a chicken patched homolog by sonic hedgehog in the developing limb," <i>Development</i> 122:1225-1233 (1996)	
	CX1	Marigo et al., "Regulation of patched by sonic hedgehog in the developing neural tube," <i>PNAS</i> 93:9346-9351 (1996)	
	CY1	Marti et al., "Requirement of 19K from the sonic hedgehog for induction of distinct ventral cell types in CNS explants," <i>Nature</i> 375:322-325 (1995)	
	CZ1	Marti et al., "Distribution of sonic hedgehog peptides in the developing chick and mouse embryo," <i>Development</i> 121:2537-2547 (1995)	
	CA2	Mitra-Kirtley et al., "Determination of the nitrogen chemical structures using XANES spectroscopy," <i>JACS</i> 115:252-258 (1993)	
	CB2	Munsterberg et al., "Combinatorial signaling by sonic hedgehog and Wnt family members induces myogenic bHLH gene expression in the somite," <i>Genes Vev.</i> 9:2911-2922 (1995)	
	CC2	Nakano et al., "A protein with several possible membrane-spanning domains encoded by drosophila segment polarity gene patched," <i>Nature</i> 341:508-513 (1989)	
	CD2	Niswander et al., "A positive feedback loop coordinates growth and patterning in the vertebrate limb," <i>Nature</i> 371:609-612 (1994)	
	CE2	Nusse, "Patching up hedgehog," <i>Nature</i> 384:119-120 (1996)	
	CF2	Omnell et al., "Expression of veratrum alkaloid teratogenicity in the mouse," <i>Teratology</i> 42:105-119 (1990)	
	CG2	Orenic et al., "Cloning and characterization of the segment polarity gene <i>cubitus interruptus</i> dominant of drosophila," <i>Genes and Development</i> 4:1053-1067 (1990)	
	CH2	Oro et al., "Basal cell carcinomas in mice overexpressing sonic hedgehog," <i>Science</i> 276:817-821 (1997)	
	CI2	Perrimon, "Hedgehog and beyond," <i>Cell</i> 80:517-520 (1995)	
	CJ2	Perrimon, "Serpentine proteins slither into the wingless and hedgehog fields," <i>Cell</i> 86:513-516 (1996)	
	CK2	Placzek et al., "Induction of floor plate differentiation by contract-dependent, homeogenetic signals," <i>Development</i> 117:205-218 (1993)	
	CL2	Porter et al., "Hedgehog patterning activity: role of a lipophilic modification mediated by the carboxy-terminal autoprocessing domain," <i>Cell</i> 86:21-34 (1996)	
	CM2	Porter et al., "The product of hedgehog autoproteolytic cleavage active in local and long-range signalling," <i>Nature</i> 374:363-366 (1995)	
	CN2	Riddle et al., "Sonic hedgehog mediates the polarizing activity of the ZPA," <i>Cell</i> 75:1401-1416 (1993)	
	CO2	Roberts et al., "Sonic hedgehog is an endodermal signal inducing Bmp-4 and Hox genes during induction and regionalization of the chick hindgut," <i>Development</i> 121:3163-3174 (1995)	
	CP2	Roelink et al., "Floor plate and motor neuron induction by different concentrations of the amino-terminal cleavage product of sonic hedgehog autoproteolysis," <i>Cell</i> 81:445-455 (1995)	
	CQ2	Roelink et al., "Floor plate and motor neuron induction by <i>vhf-1</i> , a vertebrate homolog of hedgehog expressed by the notochord," <i>Cell</i> 76:761-775 (1994)	
	CR2	Stone et al., "The tumour-suppressor gene <i>patched</i> encodes a candidate receptor for sonic hedgehog," <i>Nature</i> 384:129-134 (1996)	
	CS2	Stone et al., "Future directions," <i>Clin Orthop Relat Res</i> 252:129 (1990)	
	CT2	Tabata et al., "The drosophila hedgehog gene is expressed specifically in posterior compartment cells and is a target of engrailed regulation," <i>Genes Dev.</i> 6:2635-2645 (1992)	
	CU2	Takigawa et al., "Chondrocytes dedifferentiated by serial monolayer culture form cartilage nodules in nude mice," <i>Bone Miner</i> 2:449 (1987)	
	CV2	Tanabe et al., "Induction of motor neurons by sonic hedgehog is independent of floor plate differentiation," <i>Curr Biol.</i> 5:651-658 (1995)	
	CW2	Vacanti et al., "Synthetic polymers seeded with chondrocytes provide a template for new cartilage formation," <i>Plast Reconstr Surg</i> 88:753 (1991)	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO				<i>Complete if Known</i>	
				Application Number	Not Yet Assigned
				Filing Date	December 9, 2003
				First Named Inventor	Henryk Dudek
				Art Unit	N/A
				Examiner Name	Not Yet Assigned
Sheet	5	of	5	Attorney Docket Number	CIBT-P03-068

CX2	von Schroeder et al., "The use of polyactic acid matrix and periosteal grafts for the reconstruction of rabbit knee articular defects," J Biomed Mater Res 25:329 (1991)	
CY2	Wakitani et al., "Repair of rabbit articular surfaces with allograft chondrocytes embedded in collagen cell," J. Bone Jt Surg 71B:74 (1989)	
CZ2	Wang et al., "Induction of dopaminergic neuron phenotype in the midbrain by sonic hedgehog protein," Nature Med. 1:1184-1188 (1995)	
CA3	Weinberg et al., "Developmental regulation of zebrafish MyoD in wild-type, no tail and spadetail embryos," Development 122:271-280 (1996)	
CB3	Xie et al., "Mutations of the patched gene in several types of sporadic extracutaneous tumors," Cancer Res 57:2369-2372 (1997)	
CC3	Xie et al., "Physically mapping the 5 Mb D9S196-D9S180 interval harboring the basal cell nevus syndrome gene and localization of six genes in this region," Genes Chromosomes Cancer 18:305-309 (1997)	
CD3	Yamada et al., "Control of cell pattern in the neural tube: motor neuron induction by diffusible factors from notochord and floor plate," Cell 73:673-686 (1993)	
CE3	Murone et al., "Sonic hedgehog signaling by the patched-smoothened receptor complex," Current Biology 9:76-84 (1999)	
CF3	Epstein et al., "Antagonizing cAMP-dependent protein kinase A in the dorsal CNS activates a conserved sonic hedgehog signaling pathway," Development 122:2885-2894 (1996)	

<sup>1</sup>EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup>Applicant's unique citation designation number (optional). <sup>2</sup>Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	
--------------------	--	-----------------	--